UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,389	08/25/2000	David Pinsky	62683/JPW/JML	5890

7590 02/17/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,389	PINSKY ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-20,22-30 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16, 18-20, 22-30, and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks, filed November 13, 2003.

Claims 21 and 31 have been canceled. Claims 16, 20, 26-30 and 36 have been amended.

Claims 16, 18-20, 22-30, and 32-36 are pending in the instant application.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 16 and 27 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment to the claims to correct for lack of antecedent basis.

Claims 16, 18, 19, 20, 22-25, 27-30, and 32-35 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is withdrawn** in view of Applicant's Amendment to the claims to replace the term "compound" with "nucleic acid".

Claims 16, 18-20, 22-30, and 32-36 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with SEQ ID NO: 1 *ex vivo*, does not reasonably provide enablement for a method for reducing ischemic damage to tissue being transplanted into a subject comprising contacting the tissue with any inhibitor of Egr-1 *ex vivo*. **This rejection is withdrawn** in view of the new 35 U.S.C. 112, first paragraph rejection presented below:

Claims 16, 18-20, 22-30, and 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing ischemic damage to a lung tissue being transplanted into a subject comprising contacting the tissue with SEQ ID NO: 1 *ex vivo*, does not reasonably provide enablement for a method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 16, 18-20, 22-30, and 32-36 are drawn to a method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid that inhibits Egr-1 expression, before, during or after reperfusion.

The instant invention specification provides general methodologies for decreasing Egr-1 mRNA and protein expression in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* (see Figures 10 and 11). Additionally, the instant specification shows arterial oxygenation

(gas exchange) and survival times of rats transplanted with preserved lungs treated with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* (see Figures 12 and 13).

The unpredictability of the art of nucleic acid therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS Vol. 23, February 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend

only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Additionally, in a published review of the potential use of antisense oligonucleotides as therapeutic agents, Gewirtz et al. (Proc. Natl. Acad. Sci, 1996 Vol. 93:3161-3163) teach that the inhibitory activity of an oligonucleotide depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligonucleotide to reach its target (page 3161, second and third columns). Gewirtz et al. conclude by observing that, "the antisense approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph).

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention commensurate in scope with these claims without having to engage in trial and error or undue experimentation. The specification as filed contemplates an *in vivo* method for reducing vascular injury during reperfusion of any ischemic tissue comprising contacting the tissue with any nucleic acid which inhibits expression of Egr-1. However, the instant specification does not show any nexus between decreasing Egr-1 mRNA and protein expression and increasing survival times, and arterial oxygenation in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* and an *in vivo* method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1. It is unclear how the specific *ex vivo* data is correlated with/or representative of an *in vivo* a method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1. It is also unclear how any nucleic acid will inhibit expression of Egr-1

in vivo where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for an *in vivo* a method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1. The specification does not provide guidance for the delivery of nucleic acids into the target organ and target cells *in vivo* in quantity sufficient to inhibit Egr-1 expression. While the specification provides guidance to addressing antisense compound administration to cells and pulmonary grafts *in vitro* and *ex vivo*, the specification provides no particular nexus between an *in vivo* method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc, for nucleic acid/antisense targeting Egr-1 *in vivo*. The specification provides no particular guidance or direction for reducing vascular injury *in vivo* during reperfusion of an ischemic tissue using a polynucleotide sequence complementary to Egr-1 of the claimed invention. Without specific guidance from the specification, the skilled artisan is left to guess what nucleic acids possess activity to inhibit Egr-1 expression and to further guess what sequences would elicit an inhibitory response to Egr-1 since it cannot determined from the specification through what mechanism the oligonucleotides would exert its inhibitory activity, i.e., antisense, triplex, aptamer, or unknown mechanisms.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate in scope with these claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between decreasing Egr-1 mRNA and protein expression and increasing survival times, and arterial oxygenation in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo*, and an *in vivo* method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with any nucleic acid which inhibits the expression of Egr-1, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to target and inhibit the expression of Egr-1 *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention would include the de novo determination of how to engineer and deliver nucleic acid targeting Egr-1 *in vivo* such that vascular injury during reperfusion of an ischemic tissue would be reduced to any degree, particularly, in view of the obstacles needed to overcome to use nucleic acid therapies *in vivo* as exemplified in the references discussed above.

It is noted that in the previous Office Action, a similar 35 U.S.C. 112, first paragraph rejection was made against claims 16 and 18-36. In response to this rejection, Applicants argue that damage to the vascular tissue of an ischemic tissue, would similar to *ex vivo*, be reduced when a nucleic acid contacts the tissue *in vivo*. Applicants contend that blood vessel cells exist in tissue form *ex vivo*, as opposed to free-floating cell culture form, which render them a more

structurally and physiologically accurate model for predicting *in vivo* results. Applicants argue that because the tissue being contacted with the nucleic acid is vascular, intravenous administration of the nucleic acid would necessarily contact the vascular tissue. Applicants also argue that the Examiner has not provided any evidence indicating that the favorable results obtained with *ex vivo* vascular tissue treatment with Egr-1 would differ from results obtained with *in vivo* treatment.

Applicant's arguments have been fully considered. Regarding Applicants argument that damage to the vascular tissue of an ischemic tissue, would similar to *ex vivo*, be reduced when a nucleic acid contacts the tissue *in vivo*, this is not found persuasive. Applicants have not provided any working examples to persuade the Examiner that damage to the vascular tissue of an ischemic tissue, would similar to *ex vivo*, be reduced when a nucleic acid contacts the tissue *in vivo*. According to the discussions by Branch, Jen et al. and Gewirtz et al., *in vivo* inhibition of gene expression in the whole animal remains unpredictable and is not a matter of routine screening. Because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention commensurate in scope with these claims. Regarding Applicants argument that the Examiner has not provided any evidence indicating that the favorable results obtained with *ex vivo* vascular tissue treatment with Egr-1 would differ from results obtained with *in vivo* treatment, this is not found persuasive. The Examiner has provided three review articles discussing the unpredictability of the art of using nucleic acids in a whole animal. These review articles collectively teach that *in vivo* inhibition

of gene expression in the whole animal remains unpredictable and is not a matter of routine screening. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention commensurate in scope with these claims.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Applicant's amendment Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0564.

tcg
January 30, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER